Complete Summary

GUIDELINE TITLE

Management of ductal carcinoma in situ of the breast: a clinical practice guideline.

BIBLIOGRAPHIC SOURCE(S)

Shelley W, McCready D, Holloway C, Trudeau M, Sinclair S, Breast Cancer Disease Site Group. Management of ductal carcinoma in situ of the breast: a clinical practice guideline. Toronto (ON): Cancer Care Ontario (CCO); 2006 Sep 19. 41 p. (Evidence-based series; no. 1-10). [84 references]

GUIDELINE STATUS

This is the current release of the guideline.

The EVIDENCE-BASED SERIES report, initially the full original Guideline, over time will expand to contain new information emerging from their reviewing and updating activities.

Please visit the Cancer Care Ontario Web site for details on any new evidence that has emerged and implications to the guidelines.

COMPLETE SUMMARY CONTENT

SCOPE

DISEASE/CONDITION(S)

Ductal carcinoma in situ (DCIS) of the breast

GUIDELINE CATEGORY

Assessment of Therapeutic Effectiveness
Management
Treatment

CLINICAL SPECIALTY

Oncology
Radiation Oncology
Surgery

INTENDED USERS

Physicians

GUIDELINE OBJECTIVE(S)

- To evaluate the optimal surgical management of ductal carcinoma in situ (DCIS) of the breast
- To evaluate whether breast irradiation should be offered to women with DCIS, following breast-conserving surgery (defined as excision of the tumour with microscopically clear resection margins)
- To evaluate whether there are patients who could be spared breast irradiation post–breast-conserving surgery for DCIS
- To evaluate the role of tamoxifen in the management of DCIS

TARGET POPULATION

Women with ductal carcinoma in situ (DCIS) of the breast

INTERVENTIONS AND PRACTICES CONSIDERED

1. Total mastectomy
2. Breast-conserving surgery (lumpectomy)
3. Radiotherapy following breast-conserving surgery
4. Tamoxifen and radiotherapy versus radiotherapy alone

MAJOR OUTCOMES CONSIDERED

- Overall survival
- Disease-free survival
- Local recurrence
- Breast conservation
- Distant recurrence
- Toxicity
- Quality of life

METHODOLOGY

METHODS USED TO COLLECT/SELECT EVIDENCE

Hand-searches of Published Literature (Primary Sources)
Hand-searches of Published Literature (Secondary Sources)
Searches of Electronic Databases

DESCRIPTION OF METHODS USED TO COLLECT/SELECT THE EVIDENCE

MEDLINE was searched to March 2006, using a disease-specific medical subject heading (MeSH) term ("carcinoma, intraductal, noninfiltrating") and treatment-specific MeSH terms ("radiotherapy," "mastectomy," or "tamoxifen"). The Excerpta Medica database (EMBASE) was also searched up to March 2006, using a disease-specific Excerpta Medica Tree (EMTREE) term ("intraductal carcinoma") and the same treatment-specific EMTREE term as for the MEDLINE search.

Issue 5 (2004) of the Cochrane Library, the Physician Data Query database (http://www.cancer.gov/search/clinical_trials/), and conference proceedings from the American Society of Clinical Oncology (1998 to 2005), the American Society for Therapeutic Radiology and Oncology (1998 to 2005), and the San Antonio Breast Cancer Symposium (2001 to 2005) were also searched. The Canadian Medical Association Infobase (http://mdm.ca/cpgsnew/cpgs/index.asp) and the National Guideline Clearinghouse (http://www.guideline.gov/) were searched for existing evidence-based practice guidelines. Relevant articles and abstracts were selected and reviewed by three reviewers, and the reference lists from these sources were searched for additional trials, as were the reference lists from relevant review articles.

Inclusion Criteria

Articles were selected for inclusion in this systematic review of the evidence if they met the following criteria:

- The management of ductal carcinoma in situ (DCIS) of the breast was evaluated using a randomized controlled trial or a meta-analysis of non-randomized and/or randomized trials.
- Reported outcomes included overall or disease-free survival, local recurrence (invasive or non-invasive), breast conservation, distant recurrence, toxicity, or quality of life.
- Clinical trial results were reported in full papers or abstracts. Although data presented in meeting abstracts may not be as reliable and complete as that from papers published in peer-reviewed journals, abstracts can be a source of important evidence from randomized trials and add to the evidence available from fully published studies. These data often appear first in meeting abstracts and may not be published for several years.

Evidence-based clinical practice guidelines addressing this topic were also eligible for inclusion.

Exclusion Criteria

Articles were excluded if they met the following criteria:

- Trial results were published in a language other than English.

- Publication occurred prior to 1983. Because our understanding of ductal carcinoma in situ biology has evolved substantially since the maturation of screening mammography, trials published prior to this date are not relevant to current clinical practice.

NUMBER OF SOURCE DOCUMENTS

The following publications were eligible for inclusion in the systematic review of the evidence:

- One subgroup analysis of patients found to have ductal carcinoma in situ (DCIS) on pathology review of a randomized trial designed to address the role of breast-conserving surgery (BCS) in early-stage invasive breast cancer. Two meta-analyses on the surgical management of DCIS, comprised predominantly of non-randomized prospective and retrospective studies.
- Three randomized trials (reported in eight articles) that evaluated the use of adjuvant radiotherapy in patients who had undergone breast-conserving surgery for DCIS.
- Two randomized trials (reported in three articles) that investigated the use of tamoxifen in patients with DCIS who had undergone breast-conserving surgery and adjuvant radiotherapy.
- Six practice guidelines relevant to the management of DCIS of the breast (reported in seven sources).

METHODS USED TO ASSESS THE QUALITY AND STRENGTH OF THE EVIDENCE

Expert Consensus (Committee)

RATING SCHEME FOR THE STRENGTH OF THE EVIDENCE

Not applicable

METHODS USED TO ANALYZE THE EVIDENCE

Review of Published Meta-Analyses
Systematic Review with Evidence Tables

DESCRIPTION OF THE METHODS USED TO ANALYZE THE EVIDENCE

Because the randomized trials on the management of ductal carcinoma in situ (DCIS) of the breast were clinically heterogeneous, their results were not pooled.

METHODS USED TO FORMULATE THE RECOMMENDATIONS

Expert Consensus

DESCRIPTION OF METHODS USED TO FORMULATE THE RECOMMENDATIONS

This evidence-based series was developed by the Breast Cancer Disease Site Group (DSG) of Cancer Care Ontario's (CCO's) Program in Evidence-based Care (PEBC). The series is a convenient and up-to-date source of the best available evidence on the management of ductal carcinoma in situ (DCIS) of the breast, developed through systematic review, evidence synthesis, and input from practitioners in Ontario.

In the surgical management of DCIS, the choice between mastectomy and breast-conserving surgery (BCS) should be dependent upon patient preference and the results of clinical, mammographic, and pathologic evaluation. Mastectomy is indicated for patients at high risk of recurrence with BCS and radiation. High-risk factors include large size tumours (>5 cm), particularly those with positive margins. While optimal margin widths for patients having BCS and radiation are not specifically known, close lateral margin widths of <1 mm have been associated with higher local recurrence rates in some studies. Patients with smaller areas of DCIS with resection margins $\leq$1 mm or positive resection margins are also at a higher than average risk of recurrence. Mastectomy with the option of reconstruction is also an acceptable choice for women preferring to maximize local control. Given the importance of breast conservation for the patient and the potential for salvage, BCS and radiation is an equally acceptable option for eligible women with DCIS.

There are currently three prospective randomized trials that support the routine use of radiation following BCS for patients with DCIS of the breast. Radiation resulted in reduced rates of breast recurrence (both invasive and non-invasive) and mastectomy. Patients should be made aware of the duration of radiation and its toxicity before making a choice between total mastectomy and BCS. All three studies used the dose-fractionation schedules of 5000 cGy in 25 fractions in five weeks, which should be considered the standard; however, the Ontario Clinical Oncology Group (OCOG) randomized trial in patients with invasive breast cancer showed that the shorter fractionation schedule of 4250 cGy in 16 fractions was as effective as and no more toxic than 5000 cGy in 25 fractions. The guideline developers could find no radiobiological evidence to suggest that DCIS responds differently to radiation than invasive disease. The Breast Cancer DSG therefore felt it would be reasonable to offer this shorter fractionation schedule to those women with DCIS who preferred the convenience of a shorter overall treatment time.

None of the randomized studies in DCIS added a boost to the tumour bed. Randomized trials of boost versus no boost in patients with invasive disease have shown a decrease in local recurrence rates when a boost of 1000 to 1600 cGy is added, particularly in younger women or those with close or positive resection margins. Some DCIS studies have shown increased recurrence rates in younger women and those with close resection margins who received standard postoperative whole breast radiation without a boost. The Breast Cancer DSG therefore felt it reasonable to consider the addition of a boost to the tumour bed in those DCIS patients who are felt to be at higher than usual risk of recurrence with standard whole breast radiation alone, provided the patients are willing to accept the possibility of a somewhat poorer cosmetic outcome.

Identifying a group of patients treated with BCS for DCIS who do not require adjuvant radiotherapy is not yet possible. Current data suggest that age, tumour

size, margin status, grade, and comedo-type necrosis are important predictors for local recurrence. These studies suggest that there may be different risk groups for local failure (e.g., low, intermediate, and high) where different treatments may be more desirable—low risk, BCS alone; moderate risk, BCS plus radiation; and high risk, total mastectomy plus or minus reconstructive surgery. Further evidence is necessary before making firm recommendations and prospective randomized trials looking at this question are ongoing. Until then, it is recommended that pathologic descriptions including assessment of size, margin status, nuclear grade, and evidence of comedo necrosis be reported more consistently. Patients interested in BCS alone should be made aware of what is currently known about the potential benefits and toxicities of post-lumpectomy radiation.

The National Surgical Adjuvant Breast Project (NSABP-24) study showed an overall decrease in invasive and in situ disease with the addition of tamoxifen to surgical excision followed by radiation, but most of the benefit appeared to be in younger women and those with positive or unknown resection margins. The United Kingdom Coordinating Committee on Cancer Research (UKCCCR) study showed no benefit with the addition of tamoxifen, but the study population consisted mostly of women over 50 years of age with clear resection margins. There was an observed benefit in the subset of women less than 50 years of age and also in those who did not receive radiation. Therefore, the Breast Cancer DSG felt that five years of tamoxifen is an option for DCIS patients, particularly in women less than 50 years of age, those with positive resection margins who refuse further surgery, and those who refused or are unable to have radiation but want to avoid mastectomy. Patients and physicians need to consider the potential toxicities of tamoxifen as well as the possible benefits.

RATING SCHEME FOR THE STRENGTH OF THE RECOMMENDATIONS

Not applicable

COST ANALYSIS

A formal cost analysis was not performed and published cost analyses were not performed.

METHOD OF GUIDELINE VALIDATION

External Peer Review
Internal Peer Review

DESCRIPTION OF METHOD OF GUIDELINE VALIDATION

Report Approval Panel

Prior to the submission of this Evidence-based Series report for external review, the report was reviewed and approved by the Program in Evidence-based Care (PEBC) Report Approval Panel, which consists of two members, including an oncologist, with expertise in clinical and methodology issues. The Report Approval Panel did not identify any issues of concern and approved the report as submitted to them.

External Review by Ontario Clinicians

Following the review and discussion of Sections 1 and 2 of this evidence-based series and review and the approval of the report by the Program in Evidence-based Care Report Approval Panel, the Breast Cancer Disease Site Group (DSG) circulated the clinical practice guideline and systematic review to clinicians in Ontario for review and feedback.

Feedback was obtained through a mailed survey of 109 practitioners in Ontario, including 54 surgeons, 31 radiation oncologists, and 24 medical oncologists. The survey consisted of items evaluating the methods, results, and interpretive summary used to inform the draft recommendations and whether the draft recommendations should be approved as a practice guideline. Written comments were invited. The survey was mailed out on June 23, 2006. Follow-up reminders were sent at two weeks (post card) and four weeks (complete package mailed again). The authors reviewed the results of the survey.

RECOMMENDATIONS

MAJOR RECOMMENDATIONS

Surgical Management

- Women with ductal carcinoma in situ (DCIS) of the breast who are candidates for breast conserving surgery should be offered the choice of lumpectomy or total mastectomy.
- Mastectomy with the option for reconstruction remains an acceptable choice for women preferring to maximize local control.

Radiotherapy

- Women with ductal carcinoma in situ who have undergone breast-conserving surgery should be offered adjuvant breast irradiation.
- Randomized trials of post-lumpectomy radiation versus observation in patients at relatively low risk of recurrence following surgery alone are ongoing. Until the results of those studies are available, these patients should be referred to a radiation oncologist for a thorough discussion of what is currently known about the potential benefits and toxicities of post-lumpectomy radiation in their particular situation.

Tamoxifen

- While there is some evidence to suggest that tamoxifen is effective in the reduction of ipsilateral recurrence and contralateral incidence in women with ductal carcinoma in situ, the absolute benefit is small and the evidence is conflicting.
- Women should be informed of the option of five years of tamoxifen therapy and of the potential toxicities and benefits associated with tamoxifen.

CLINICAL ALGORITHM(S)

None provided

EVIDENCE SUPPORTING THE RECOMMENDATIONS

TYPE OF EVIDENCE SUPPORTING THE RECOMMENDATIONS

The recommendations are supported by meta-analyses, randomized controlled trials, practice guidelines, and one subgroup analysis.

BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS

POTENTIAL BENEFITS

- No randomized trials designed to compare total mastectomy with breast-conserving surgery for ductal carcinoma is situ (DCIS) were found. The National Surgical Adjuvant Breast Project (NSABP) B-06 trial involved women with invasive malignancy. However, a small number of women entered were found, on pathology review, to have only DCIS. An analysis based on this subgroup of DCIS patients found a trend towards a much higher local recurrence rate in patients who received breast-conserving surgery alone (9/21; 43%), compared with those who received either breast-conserving surgery plus radiotherapy (2/27; 7%) or mastectomy (0/28; 0%). Two meta-analyses, consisting mainly of non-randomized trials, also demonstrated higher local recurrence in patients treated by breast-conserving surgery alone versus those treated by mastectomy. One reported no significant differences in local recurrence rates between patients treated by breast-conserving surgery followed by radiotherapy and mastectomy, whereas the second showed improved local recurrence rates with mastectomy. To date, no survival benefit for either type of surgery has been reported. The expert opinion of the Breast Cancer Disease Site Group (DSG) is that this non-randomized data supports the recommendation that breast-conserving surgery followed by radiation is an acceptable treatment option, in addition to mastectomy.
- Three randomized trials investigated the role of radiotherapy after breast-conserving surgery in patients with DCIS. In each, the risk of invasive and non-invasive ipsilateral recurrence was reduced with adjuvant radiotherapy. There were no significant differences in distant metastasis or overall survival.
- Two trials investigated the role of tamoxifen versus no tamoxifen in addition to breast-conserving surgery and radiotherapy in the treatment of DCIS. The first demonstrated a significantly lower cumulative incidence of ipsilateral or contralateral breast malignancy for patients in the tamoxifen group versus those in the placebo group. In the second, tamoxifen treatment did not significantly reduce the incidence of either ipsilateral or contralateral breast malignancy.

POTENTIAL HARMS

Radiation Therapy

In one study comparing two different fractionation schedules, grade 2 or 3 skin toxicity was 66% in the 16-fraction arm and 60% in the 25-fraction arm (absolute

difference, 6%; 95% CI, -0.3% to 10%). Four cases of radiation pneumonitis (two in each arm) and one case of rib fracture (in the 25-fraction arm) occurred.

Tamoxifen

The following toxicities were observed in one study of tamoxifen versus placebo:

- Endometrial cancer
- Stroke
- Pulmonary embolism
- Deep vein thrombosis

CONTRAINDICATIONS

CONTRAINDICATIONS

As with invasive disease, there are a number of contraindications for breast-conserving surgery (BCS). Patients with large tumours or small breasts may not have a satisfactory cosmetic result and may be better served by a simple mastectomy with the option of breast reconstruction. Also, patients with ductal carcinoma in situ (DCIS) >5 cm were not included in the European Organization for Research and Treatment of Cancer (EORTC) study, and only four patients in the National Surgical Adjuvant Breast Project (NSABP) B-17 study had lesions greater than 3 cm. In the NSABP B-24 study, only 4% of patients had lesions greater than 2 cm. Therefore, the local control rates reported in these studies may not be generalizable to patients with larger lesions. The presence of multiple tumours in the breast and the appearance of extensive microcalcifications are also relative contraindications to breast-conserving therapy.

QUALIFYING STATEMENTS

QUALIFYING STATEMENTS

- When breast-conserving surgery is performed, all mammographically suspicious calcifications should be removed and margins should be microscopically clear of ductal carcinoma in situ (DCIS).
- Mastectomy, with the option of reconstruction, is recommended for those women who have an area of ductal carcinoma in situ large enough that breast-conserving surgery would leave them with an unacceptable cosmetic result.
- In a subset analysis of one of the randomized studies, the beneficial effect of tamoxifen was most apparent in the estrogen receptor-positive patients. Therefore, if it is felt that a patient might benefit from tamoxifen for one of the reasons listed in the original guideline document, hormone receptor assessment could be considered in order to aid in the decision regarding tamoxifen treatment.
- Randomized studies suggest that women who are most likely to have a positive benefit/risk ratio with tamoxifen are those who are less than 50 years of age or who have positive resection margins and refuse further surgery. Women who have a contraindication to radiation or who refuse this treatment

but still want to avoid mastectomy should also be considered for tamoxifen therapy.
- Care has been taken in the preparation of the information contained in this document. Nonetheless, any person seeking to apply or consult the evidence-based series is expected to use independent medical judgment in the context of individual clinical circumstances or seek out the supervision of a qualified clinician. Cancer Care Ontario makes no representation or guarantees of any kind whatsoever regarding their content or use or application and disclaims any for their application or use in any way.

IMPLEMENTATION OF THE GUIDELINE

DESCRIPTION OF IMPLEMENTATION STRATEGY

An implementation strategy was not provided.

INSTITUTE OF MEDICINE (IOM) NATIONAL HEALTHCARE QUALITY REPORT CATEGORIES

IOM CARE NEED

Living with Illness

IOM DOMAIN

Effectiveness

IDENTIFYING INFORMATION AND AVAILABILITY

BIBLIOGRAPHIC SOURCE(S)

Shelley W, McCready D, Holloway C, Trudeau M, Sinclair S, Breast Cancer Disease Site Group. Management of ductal carcinoma in situ of the breast: a clinical practice guideline. Toronto (ON): Cancer Care Ontario (CCO); 2006 Sep 19. 41 p. (Evidence-based series; no. 1-10). [84 references]

ADAPTATION

Not applicable: The guideline was not adapted from another source.

DATE RELEASED

1998 Jan 20 (revised 2006 Sep 19)

GUIDELINE DEVELOPER(S)

Program in Evidence-based Care - State/Local Government Agency [Non-U.S.]

GUIDELINE DEVELOPER COMMENT

The Program in Evidence-based Care (PEBC) is a Province of Ontario initiative sponsored by Cancer Care Ontario and the Ontario Ministry of Health and Long-Term Care.

SOURCE(S) OF FUNDING

Cancer Care Ontario
Ontario Ministry of Health and Long-Term Care

GUIDELINE COMMITTEE

Provincial Breast Cancer Disease Site Group

COMPOSITION OF GROUP THAT AUTHORED THE GUIDELINE

For a current list of past and present members, please see the Cancer Care Ontario Web site.

FINANCIAL DISCLOSURES/CONFLICTS OF INTEREST

None of the authors declared any potential or actual conflict of interest.

GUIDELINE STATUS

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GUIDELINE AVAILABILITY

Electronic copies: Available in Portable Document Format (PDF) from the Cancer Care Ontario Web site.

AVAILABILITY OF COMPANION DOCUMENTS

The following are available:

- Management of ductal carcinoma in situ of the breast: a clinical practice guideline summary. Toronto (ON): Cancer Care Ontario (CCO). 2006 Sep 19. Various p. (Evidence-based Series #1-10) Electronic copies: Available in Portable Document Format (PDF) from the Cancer Care Ontario Web site.
- Browman GP, Levine MN, Mohide EA, Hayward RSA, Pritchard KI, Gafni A, et al. The practice guidelines development cycle: a conceptual tool for practice guidelines development and implementation. J Clin Oncol 1995;13(2):502-12.

PATIENT RESOURCES

None available

NGC STATUS

This summary was completed by ECRI on August 19, 1999. The information was verified by the guideline developer as of September 17, 1999. This summary was updated by ECRI on July 3, 2001, July 5, 2002, July 21, 2003, and on November 30, 2006. The most recently updated information was verified by the guideline developer on January 19, 2007.

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